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Steroid responsive subacute cerebellar ataxia in a patient with Lambert-Eaton myasthenic syndrome without cancer developing after intracranial aneurysm surgery

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Abstract

Several reports have presented patients with subacute cerebellar ataxia (subacute CA) and Lambert-Eaton myasthenic syndrome (LEMS). Some clinical features of those patients have been described in the previous reports, such as priority of subacute CA to LEMS or a concurrent occurrence of both diseases, a high incidence of malignancy, less efficacy of the treatment for subacute CA compared with that for LEMS. Cerebellar ataxia in some patients with LEMS has been demonstrated to be caused by serum antibodies to P/Q-type voltage-gated calcium channels (VGCCs). Here, we report a 63-year-old woman with subacute CA and LEMS. Cerebellar ataxia appeared 15 months after the incidence of LEMS, and the onset of cerebellar ataxia was thought to be due to serum anti-P/Q-type VGCCs antibodies. The clinical course of this patient was atypical in that 1) LEMS preceded subacute CA which developed after intracranial aneurysm surgery, 2) no malignancy was detected when both diseases coexisted, 3) symptoms of LEMS did not progress with the onset of cerebellar ataxia, and 4) cerebellar ataxia showed a definite improvement in symptoms and by $^{123}$I-IMP SPECT imaging after steroid administration. In addition, it is remarkable that LEMS became aggravated in electrophysiological examinations in contrast to subacute CA. We suggest that these atypical features of subacute CA and the changes in LEMS may be associated with a balance between the amount of serum anti-P/Q-type VGCCs antibodies and the susceptibility of the cerebellum and presynaptic nerve terminals to the antibodies. More cases are needed to investigate the mechanisms involved. The subacute CA and LEMS in this patient have remained comparatively silent after the withdrawal of steroid, and we are continuing to observe her condition.
Introduction

Lambert-Eaton myasthenic syndrome (LEMS) and subacute cerebellar ataxia (subacute CA) consist of paraneoplastic neurological syndromes. Occasionally, they have been reported to coexist in individual patients. These patients have cancers with high frequency and subacute CA is thought to be caused by autoantibodies against antigens coexpressed by the cancers and by neurons associated with LEMS. As a treatment to the coexistence of cerebellar ataxia and LEMS, usually cancer reduction is selected. In addition, 3,4-Diaminopyridine, steroids, or immunosuppressants are often administered, and plasmapheresis is attempted. Subacute CA has been reported to be less responsive to these treatments than LEMS.

We encountered a patient with an onset of LEMS at 62 years old, followed by subacute CA after 15 months. The subacute CA developed four months after intracranial aneurysm surgery. No malignancies were observed when subacute CA occurred. Steroid administration greatly improved the cerebellar ataxia. Since our patient has several atypical features compared with reported cases, we present our case here and examine its clinical course.

Case presentation

A 62 year-old woman developed weakness in the distal portion of her lower limbs. This symptom slowly progressed to the proximal portion until she required a walker to assist herself while ambulating. Proximal weakness in the upper limbs followed after 4 months. She was admitted to
our hospital. Her neurological examination demonstrated thirst, diplopia on leftward gaze, weakness of four extremities with proximal dominance, diminished deep tendon reflexes of four extremities, post-tetanic potentiation of right biceps bracii tendon reflex, and a waddling gait with help. Nerve conduction studies (NCS) in stimulating the left ulnar nerve and detection by surface electrodes overlying the left abductor digiti minimi (ADM) showed low amplitude of the distal compound muscle action potential (CMAP, 0.69 mV) and marked waxing (>500%) at a stimulation rate of 100 Hz. The serum titer of anti-P/Q-type voltage-gated calcium channels (VGCCs) antibodies was 59.3 pmol/L (cutoff value, <20 pmol/L). Therefore, her diagnosis was LEMS. Systemic investigation detected no malignancies. 3,4-Diaminopyridine (3,4-DAP) was prescribed after approval of its administration by the ethics committee of Hokkaido University Graduate School of Medicine. It was administered at 80 mg/day for a few months. Pyridostigmine bromide 180 mg/day was also administered. Weakness slowly improved and she became able to walk with a walker after one month. After six months, she developed an aneurysm at the M2 segment of the right middle cerebral artery, and it was clipped. After the general anesthesia for the operation, her weakness became worse. However, the 3,4-DAP and pyridostigmine bromide improved the symptoms to the pre-operation state without a dosage increment, and she was discharged.

After two months from discharge, she presented with progressing dysarthria, diplopia, clumsiness of four limbs, and truncal instability. Communicating with others, writing, and walking with support had become difficult within the past 2 weeks. Therefore, she was readmitted to our hospital. In neurological examination, slurred speech, gaze nystagmus, dysmetria of four extremities, and
severe truncal ataxia were observed. Hyporeflexia and mild proximal weakness of four extremities were unchanged from those at the time of discharge from our hospital. Electrophysiological examination of the left ulnar nerve measured on the left ADM demonstrated a greater distal CMAP (2.7 mV) and milder waxing (136 %) at 100 Hz repetitive stimulation than those observed before treatment at the first admission. In serum tests, autoantibodies associated with autoimmune systemic vasculitis (anti-nuclear, anti-DNA, anti-Sm, anti-RNP, anti-SSA, and anti-SSB antibody) were negative. Anti-GAD and anti-gliadin antibody showed no significant rise. Though anti-thyroglobulin and anti-thyroidperoxidase antibodies showed high titers (respectively 5.22 U/ml and 23.92 U/ml), anti-β-enolase antibody was within the normal range. Serum titers of onconeural antibodies (anti-Yo, anti-Ri, anti-Hu, anti-CV-2, anti-Tr, anti-Ma-2, and anti-amphiphysin antibody) were negative, but the anti-P/Q-type VGCCs antibody titer demonstrated a mild elevation (128.6 pmol/L) compared with that observed at the first examination. Tumor markers (CEA, CA19-9, SCC, Pro-GRP, NSE, NCC-ST-439, CA15-3, CA125, and soluble IL-2 receptor) in the serum were within the normal range. Cerebrospinal fluid (CSF) examination disclosed an elevation of protein (42 mg/dl), a high IgG Index (0.80) without pleocytosis (2 / μl), glucose decrement (59 mg/dl), a significant rise of titers of anti-virus antibody (to HSV, VZV, EBV, and CMV) and malignant cells. In the CSF, anti-P/Q-type VGCCs antibodies were not detected. A systemic imaging study (neck, chest, abdominal and pelvic CT, gastrofiberscope, colonfiberscope, mammography, and FDG-PET) demonstrated no evidence of cancers. Brain MRI showed no significant abnormalities except a slight bilateral cerebellar atrophy (Fig.1). ¹²³I-IMP SPECT
depicted marked hypoperfusion of the bilateral cerebellar hemispheres (Fig. 2A).

We began to administer 1 g intravenous methylprednisolone for 3 days. Afterward, we prescribed 60 mg/day (1 mg/kg) of oral prednisolone and tapered the dosage 10 mg/day every 2 weeks to 0 mg/day at 12 weeks. This treatment improved the slurred speech, nystagmus, and limb and truncal ataxia. Her condition was estimated from 53 to 39 by the International Cooperative Ataxia Rating Scale (ICARS) and from 50 to 65 by the Barthel Index (BI) for these 12 weeks. Her speech and writing became recognizable, and she became able to walk with a walker. While the slight cerebellar atrophy remained in MRI, $^{123}$I-IMP SPECT showed recovering cerebellar blood flow (Fig.2B). Approximately 12 weeks after beginning steroid administration, no cancers were detected by systemic CT and FDG-PET. Electrophysiological studies on the ADM by stimulating the left ulnar nerve showed a decrease in the distal CMAP (0.6 mV) and increment of waxing (385 %) at 100 Hz repetitive stimulations at 4 weeks after the beginning of the treatment. However, weakness of the neck and limbs were unchanged through the course of treatment, only leaving a mild proximal weakness.

She has maintained this activity of daily living without recrudescence of the cerebellar ataxia and exacerbation of weakness after withdrawal of steroid. The same dose of 3,4-DAP and pyridostigmine bromide has been continued until the present.
Discussion

In this case, subacute CA occurred at 15 months after the onset of LEMS and developed four months after intracranial aneurysm surgery. Subacute CA was the primary disorder to be investigated and treated. The likelihood that the etiology of this subacute CA is a direct tumor invasion of the cerebellum, degenerative, cerebrovascular, infectious, or systemic autoimmune inflammatory disease is remote from the results of our examinations. Hashimoto’s encephalopathy or ataxia associated with anti-gliadin antibody or anti-GAD antibody was also ruled out. We considered that the cause of this subacute CA was analogous with that of paraneoplastic cerebellar ataxia (PCA). PCA results from an autoimmune mechanism that is mediated by autoantibodies resulting in cerebellum damage. While no onconeuronal antibodies in serum were detected in our case, we suggest that this subacute CA was caused by serum anti-P/Q-type VGCCs antibodies, as shown previously 1.

According to previous reports, subacute CA-LEMS patients tend to worsen with cerebellar ataxia or to initially present symptoms of both diseases. There have been only 2 reported cases with LEMS that preceded subacute CA 2,3. In this respect, our patient is a rare case. Although the interval between the onsets of both diseases seemed longer in our case than those previously reported, an examination of similar cases is needed.

Our patient showed mild change in the anti-P/Q-type VGCCs antibody titer in serum at the second admission, but these antibodies were not detected in CSF. Therefore, we suggest that the production of anti-P/Q-type VGCCs antibodies and rise of its titer in serum may be a trigger for the occurrence
of subacute CA in LEMS patients. The detection of these antibodies in CSF has been reported in only one of five cases in which investigations in CSF were conducted $^{1,2}$. Therefore, its titer in CSF seems of little diagnostic significance at present. However, cerebellar ataxia in our case developed after intracranial aneurysm surgery. This fact may indicate that the operation influenced the function of the blood-brain barrier (BBB) and promoted circulating anti-P/Q-type VGCCs antibodies to pass through BBB, though anti-P/Q-type VGCCs antibodies in CSF within a few weeks after the neurosurgical operation could not be examined unfortunately.

In most cases of subacute CA with LEMS, cancers are detected and small cell lung cancer (SCLC) is the most common $^{1,3,4,5,6,7}$. However, our patient revealed no malignancies when examined after presenting with subacute CA and at 3 months after the beginning of steroid administration. These observations indicate another autoimmune mechanism that produces anti-P/Q-type VGCCs antibodies, other than that based on molecular mimicry between P/Q-type VGCCs and antigens expressed at the surface of cancer cells.

In previous reports of subacute CA-LEMS, subacute CA has shown little efficacy to various treatments $^{1,2,4,6}$. PCA without LEMS is also considered unlikely to have a fully effective treatment in general $^8$. However, the cerebellar ataxia in our patient was definitely improved by steroid administration, as quantitatively estimated through ICARS and BI. In addition, $^{123}$I-IMP SPECT revealed an increase of blood flow in the cerebellum after treatment (Fig.2B). The histological cerebellar damage may have remained mild in our case, although 2 months passed after the onset of subacute CA. Two months is a comparatively long time for PCA, which is considered to cause
irreversible damage in the early stage⁴. One of the factors associated with the extent of cerebellar
damage may be the balance between the amount of anti-P/Q-type VGCCs antibodies in serum and
the susceptibility of cerebellar tissue to these antibodies. However, the characteristics of
susceptibility are unknown.

In our case, LEMS had not been worsened as assessed by the physical and electrophysiological
examination, in spite of a rise in the titer of the anti-P/Q-type VGCCs antibodies in serum when
subacute CA began. This discrepancy may also be associated with the susceptibility of P/Q type
VGCCs at presynaptic nerve terminals to the antibodies. While subacute CA was improved by
steroid administration at 1 month after the start of treatment, LEMS showed subclinical
deterioration in electrophysiological tests. This observation was also difficult to explain. It is rare
that only the cerebellar ataxia improved by treatment in a subacute CA-LEMS patient⁵,⁷. In order to
reveal the causes of these phenomena, we need to examine the titer of anti-P/Q-type VGCCs
antibodies in serum after steroid administration in additional cases.

Although our case showed many atypical features compared with subacute CA-LEMS cases
reported previously, this may be due to the scarcity of information. In fact, there may be more
cancer-free subacute CA-LEMS patients with treatable cerebellar ataxia than expected. The clinical
features of our case indicate the treatability of cerebellar ataxia, the molecular mechanisms involved,
and a treatment regimen with no concern for the occurrence of malignancies.
References


Legends

Fig. 1. Brain MRI (1.5T FLAIR) of our patient.
Symmetrical dilation of cerebellar fissure indicating mild cerebellar atrophy

Fig. 2. $^{123}$I-IMP SPECT of our patient.

$^{123}$I-IMP SPECT shows hypoperfusion of bilateral cerebellar hemispheres when subacute cerebellar ataxia occurred (A). At one month after the beginning of the administration of steroid, cerebellar blood flow was increased (B).
Symmetrical dilation of cerebellar fissure indicating mild cerebellar atrophy
Fig. 2  $^{123}$I-IMP SPECT of our patient

A: Before steroid treatment

B: After steroid treatment

$^{123}$I-IMP SPECT shows hypoperfusion of bilateral cerebellar hemispheres when subacute cerebellar ataxia occurred (A). At one month after the beginning of the administration of steroid, cerebellar blood flow was increased (B).